METABOLON

Metabolon Presentation

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About Metabolon

Advancing the field of metabolomics by pioneering and patenting the industry's leading biochemical biomarker discovery and profiling platform

- **Initial funding in 2003, raised $45 million to date**
  - Sevin Rosen, Harris & Harris, Syngenta Ventures, Aurora Funds, Fletcher Spaght, Fulcrum Financial, Keating Capital Inc.
- **+60 million in bookings to date**
- **+100 staff (40 PhDs) in Research Triangle Park, NC**
- **Transformational technology marries software, know-how and biochemical biomarker discovery**

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Company Key Points

- **Validated, pioneering technology poised to transform disease treatment and diagnosis**
  - Strong IP protection with more than 100 patents filed, 17 issued
- **Profitable Metabalytics™ division growing rapidly with high repeat business from a Who's Who of pharma and biotech**
  - Ex-U.S. expansion provides further growth opportunity
- **Technology and know-how also being applied to rapidly develop a robust diagnostics pipeline**
  - Products help prevent disease with significant long-term costs, or affect patient management
  - Targeting 2 largest markets: type 2 diabetes and oncology
- **+50 peer-reviewed scientific papers published in the last 3 years.**

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Two Commercialization Paths

Metabolytics

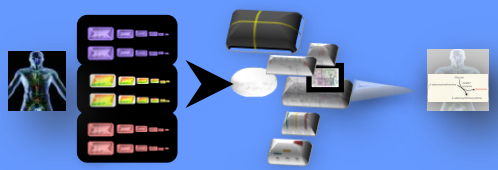
Biomarker Discovery
- mVision
- mView
- mSelect

Biomarker Monitoring
- mFocus
- Quantose IR

BioProcessMonitoring
- COP

Pharma, Biotech, Nutrition, Agri, University, Org

Metabolomics Platform Technology



Diagnostics

Pipeline
- Quantose
- Prostarix DRE
- Prostarix
- Bladder cancer aggression
- RCC aggression

Patient Monitoring
- Cisplatin

Physicians and Patients

2010 $14 Million
2011 $20 Million

Long-Term Value Creation

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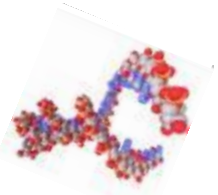
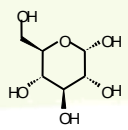
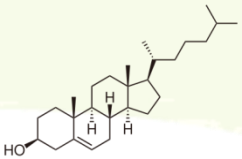
Focus on Metabolism

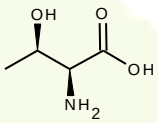




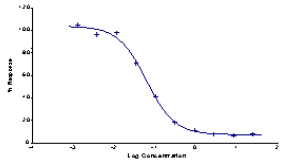
glucose

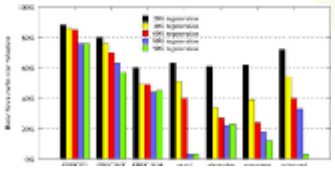


cholesterol



L-threonine





DNA

RNA

Proteins

Metabolism

Disease Mechanism

<u>Biochemistry Advantages</u>

Any sample type

Many applications

Fewer total biochemicals

Solutions through Understanding Metabolism

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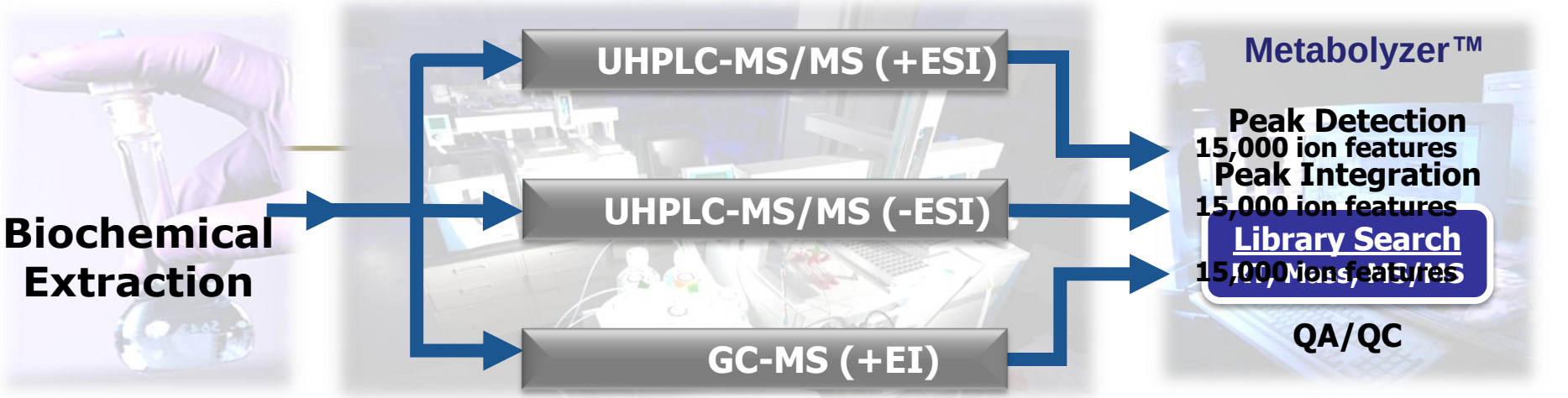
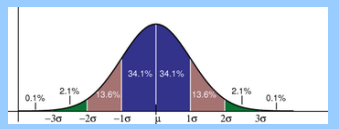


Metabolon Platform Technology



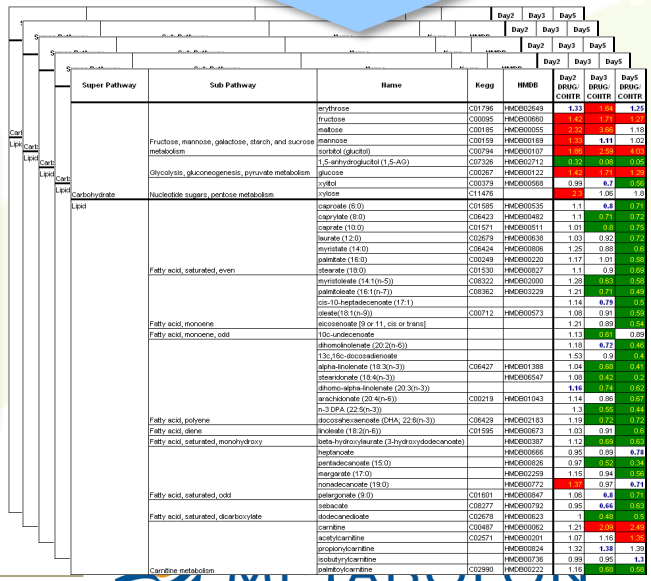
Statistical Analysis

Global Effects on Metabolism

Disease Biomarkers
Mechanistic Toxicology
Drug MOA
Cellular Characteristics

Data Interpretation

- 100's of Studies
- Institutional Knowledge
- Expert Biochemists



Heat Maps by Pathway

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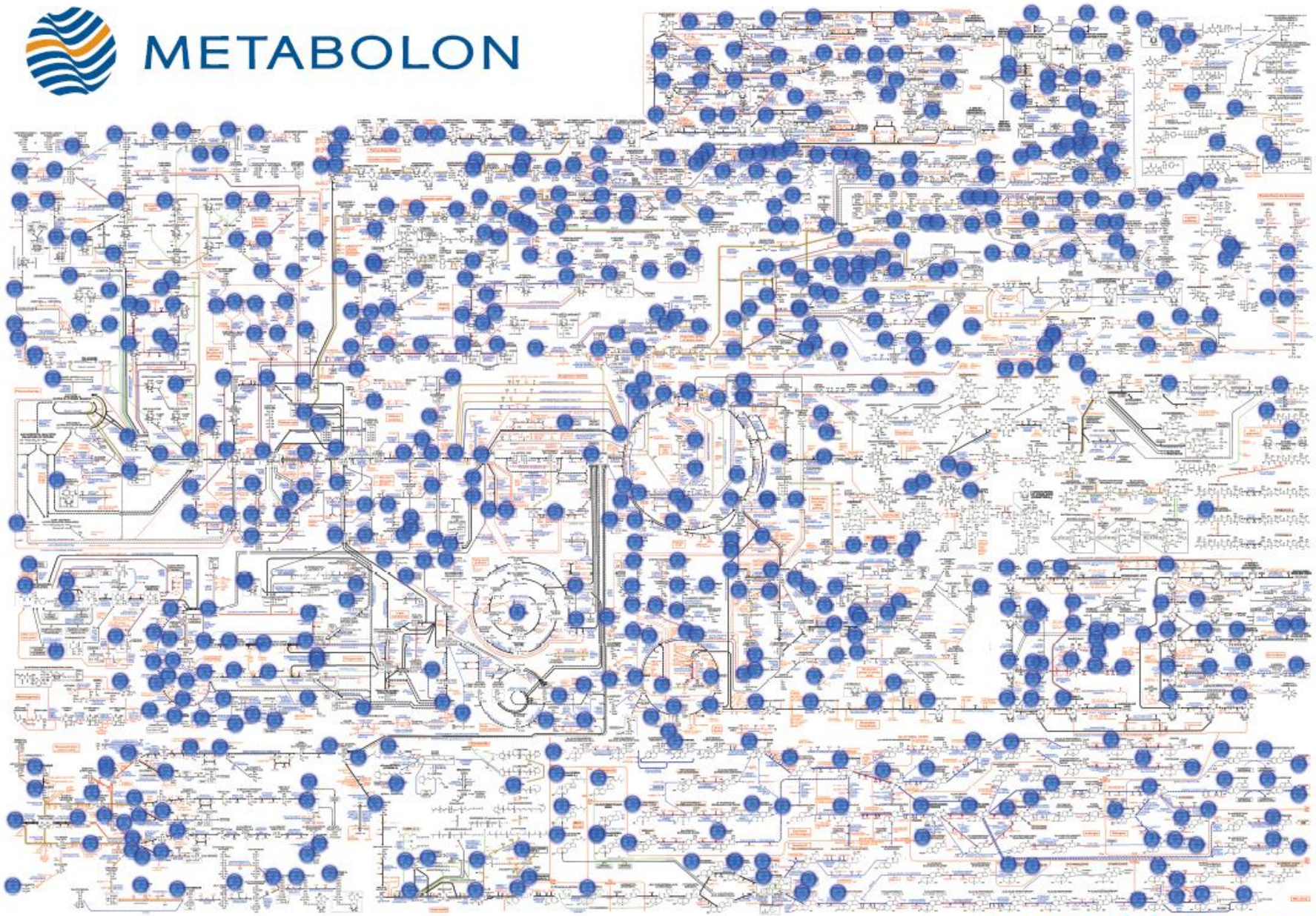

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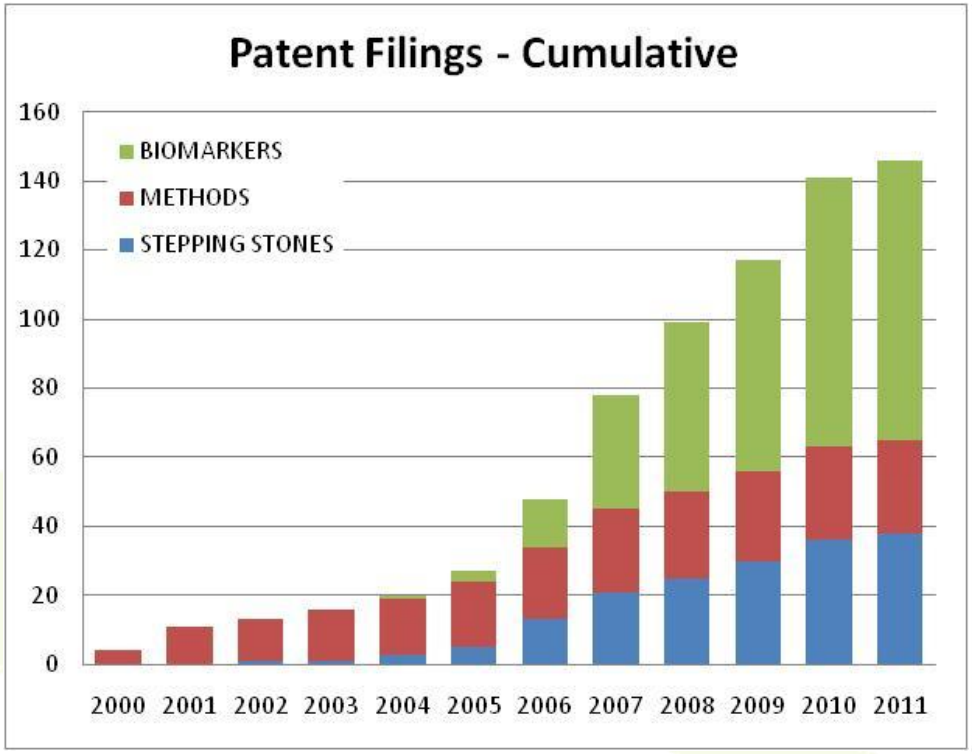
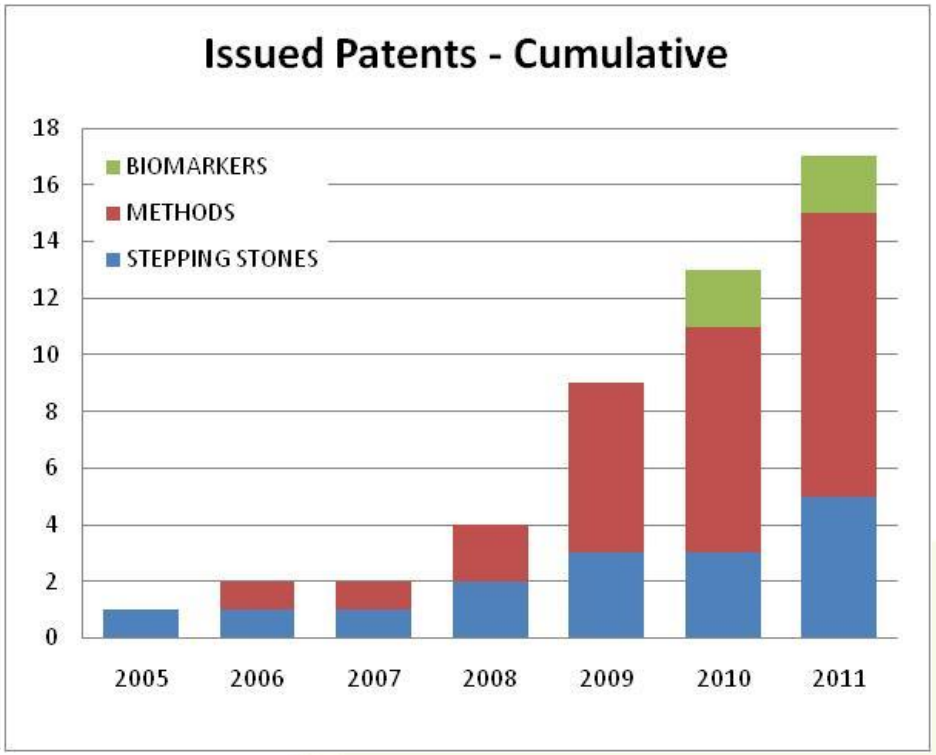
Intellectual Property





- **Methods - Fundamental IP provided by pioneering patents, first filed in 2000**
- **'Stepping Stone' Patents - Data analysis and analytical platform inventions**
- **Growing Biomarker Patent Portfolio:**

  Issued and Pending patents for biomarkers of toxicity and diseases including:

  Cancer, Insulin Resistance, Liver disease and Liver toxicity

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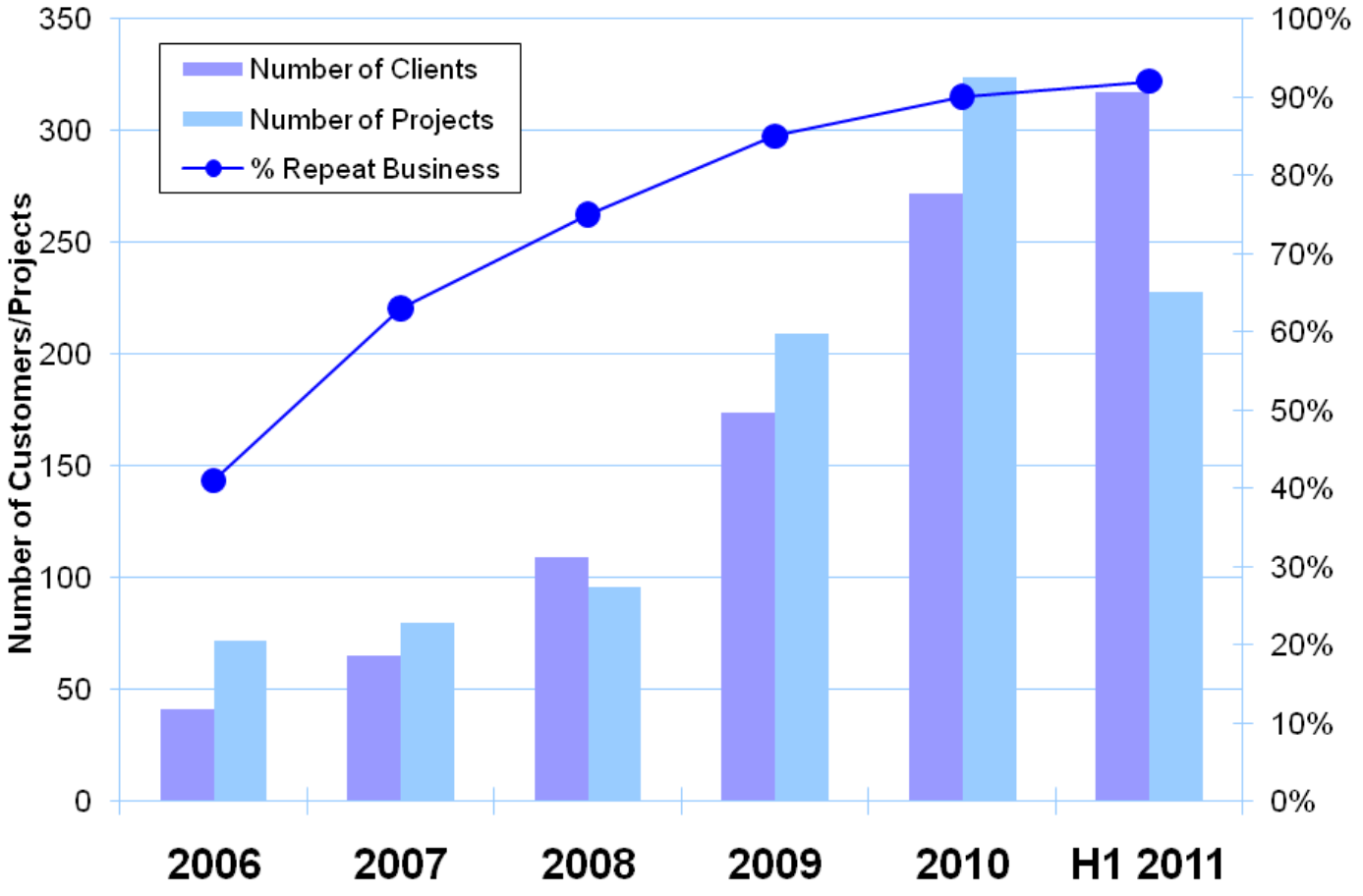
Metabolytics Business
Significant Customer Growth



$60MM Cumulative Bookings

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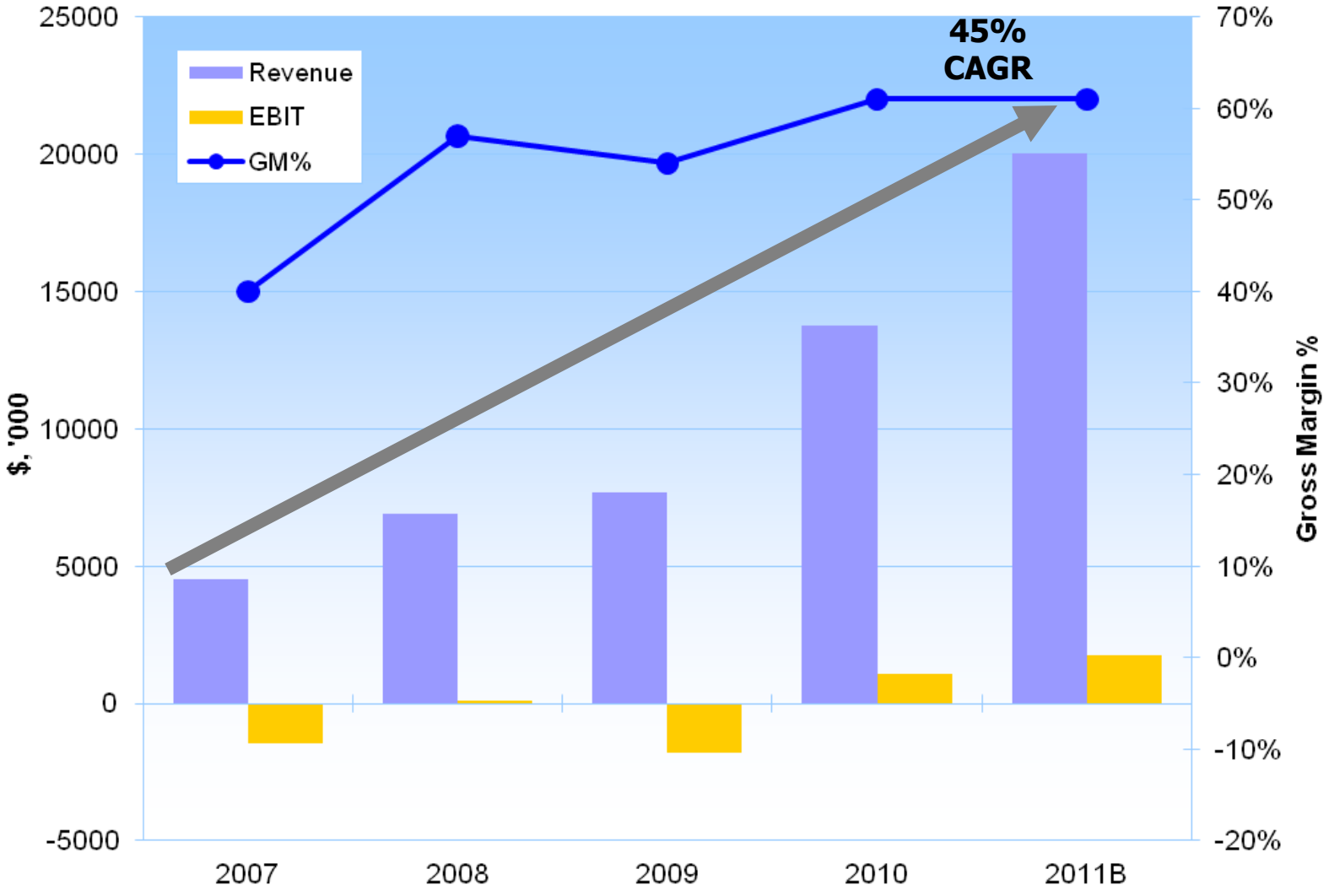
Metabolytics Business
Financial Growth



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Who's Who Customer Base

Metabolytics

Biomarker Discovery
- *mVision*
- *mView*
- *mSelect*

Biomarker Monitoring
- *mFocus*
- *Quantose IR*

BioProcess
- *COP*

Pharma, Biotech, Nutrition, Agri University, Org

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Metabolon
Diagnostics Division

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Diagnostics Business Strategy

- **Quantose™ insulin resistance test developed through commercial partnering and targeted business segments**

- **Develop a fully integrated diagnostics business utilizing our understanding of cancer metabolism**

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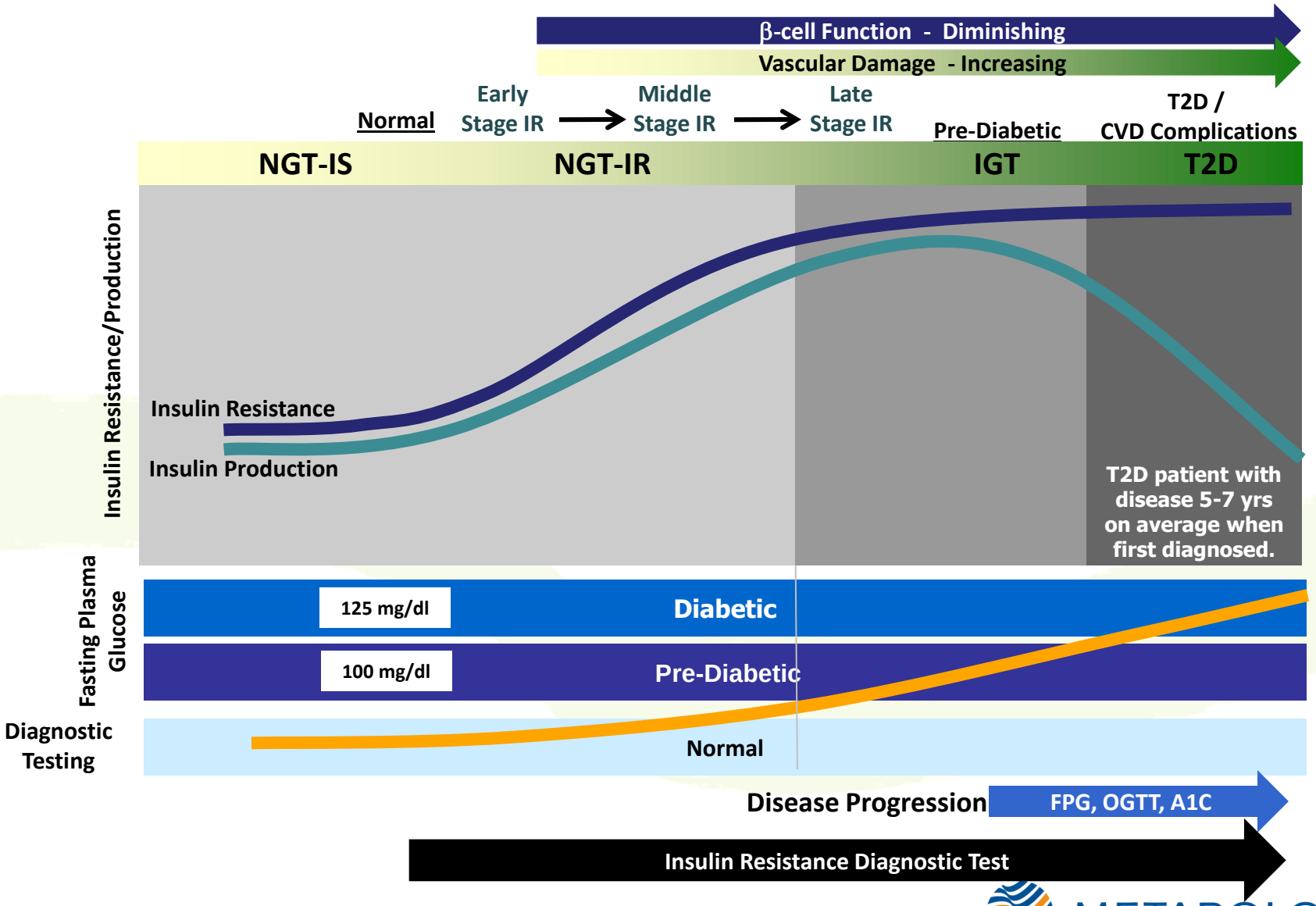
Current Glycemic Diagnostics Do Not Measure IR



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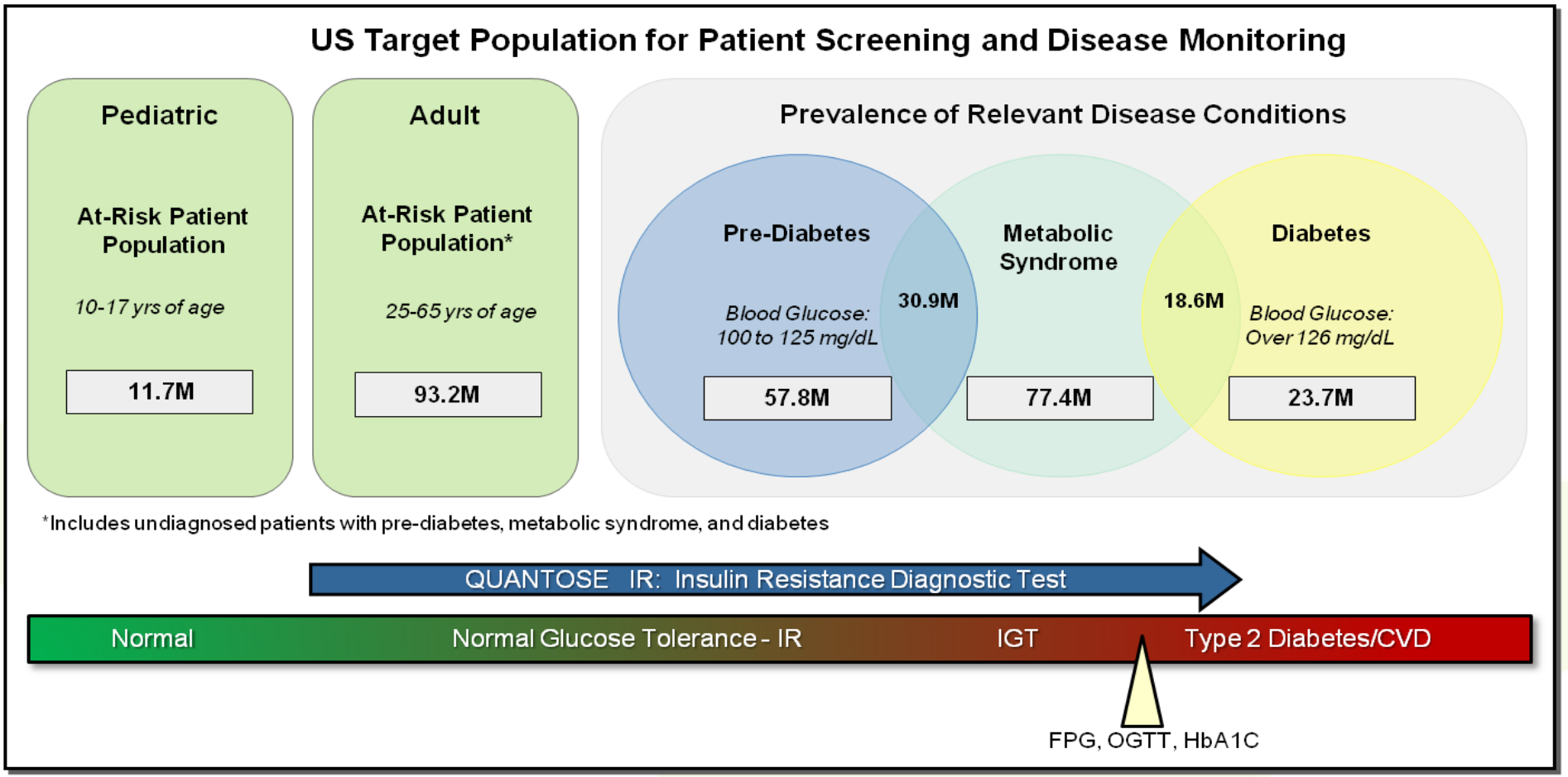
Quantose Market Opportunity



Sources: NDIC 2009; Ervin RB. 2009; CDC, 2007; US Census 2000

33% of the population in the developed world considered "at risk"

Quantose peak royalty revenue potential ~$300M if one third of at risk patients get tested annually in the US alone

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Quantose: Intended Use

Fasting plasma test to determine the risk of diabetes in 5 years

Monitors biomarkers for insulin resistance discovered and validated in collaboration with top internationally recognized KOL's

Earliest indication of Type 2 diabetes

Measures the current status of IR and how that affects diabetes risk.

Monitors health improvements from life style and drug interventions .

Targets "at risk" patients with BMI of 26 to 32

5% of patients monitoring their risk with Quantose improve their condition through more aggressive intervention

More effective than any other measure in changing patient outcome

PATIENT INFORMATION

Date: 09/16/2010
Name: John C. Smith
DOB: 11/4/1960
Patient ID: 123-45-6789
Patient address:

Ethnicity: Caucasian
Age: 49
Sex: Male
Weight: 215 lb
Height:
BMI: 28.8 kg/m²
Family History T2DM: Yes

PHYSICIAN INFORMATION

Physician Name Physician
Address PCP Phone Number
PCP Fax

SPECIMEN DESCRIPTION

Fasted EDTA plasma

ASSAY DESCRIPTION

Quantose IR is a fasting blood test for insulin resistance (IR) that is based on a panel of markers. Insulin resistance is a condition in which the natural hormone insulin becomes less effective at lowering blood sugars. Specifically, the cells that use insulin become less sensitive to insulin's effects (low insulin sensitivity or high IR). Insulin Resistance is a recognized risk factor and predictor of type II diabetes and cardiovascular disease. The test results give a probability IR score to aid a physician in identifying high-risk, dysmetabolic IR patients earlier to more effectively prevent or delay metabolic disease progression related to IR. The bottom tertile of insulin sensitivity in a general non-diabetic population is < 5 mg/kg/min rate of glucose metabolism, whereas the upper 40% of insulin sensitivity (normal range) is > 7.5 mg/kg/min.

RESULTS

Diagnostic History

Date	M value*	IR Probability	FPG (mg/dL)	BMI (kg/m²)
8/12/2009	6.3	45%	94	26.9
12/02/2010	5.1	61%	98	27.6
05/01/2011	4.5	89%	95	28.8

CURRENT IR PROBABILITY SCORE: 81%

Predicted M Value (Glucose Uptake Rate): 4.51 mg/kg/min
Prediction Confidence Intervals: 4.12 – 5.14 mg/kg/min
Predicted Diabetes Risk Assessment Score: XX% predicted risk of diabetes progression in 5 years

TEST RESULTS SUMMARY

IR probability > XX%; classified as highly insulin resistant (i.e. below bottom quartile of insulin sensitivity in a general non-diabetic population)

ANALYTE	CONCENTRATION	ODDS RATIOS FOR DISEASE RISK*
AHB (Alpha-hydroxybutyrate) 6.8 µg/ml	Insulin sensitive <3.8 µg/ml Intermediate 3.8-5 µg/ml Insulin resistant >5.0 µg/ml	
L-GPC (Linoleoyl-glycerophosphocholine) 12.7 µg/ml	Insulin sensitive >16.8 µg/ml Intermediate 13-16.8 µg/ml Insulin resistant <13 µg/ml	
Oleic Acid 103.2 µg/ml	Insulin sensitive <73.5 µg/ml Intermediate 73.5-92.0 µg/ml Insulin resistant >92.0 µg/ml	

Lit. Ref.: Gall et al. *PLoS One* May 28; 5(5):e10883 (2010). *Data on file including odds ratios and predictiveness of T2D progression.

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Cancer Diagnostics Business Strategy

- **Develop a fully integrated diagnostics business utilizing our understanding of cancer metabolism**
  - Tests focus on treatment management of cancer patients
  - Target significant underserved medical needs
  - Reduce healthcare costs while improving patient care
  - Build internal salesforce to call on urologists/oncologists
  - Run tests through CLIA laboratory to ensure quality, capture economics, build customer relationships

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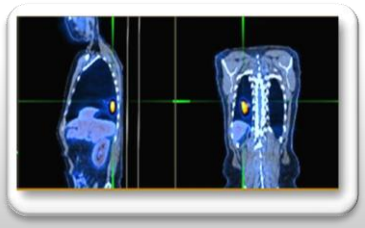
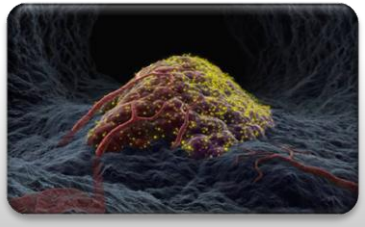
Science of Cancer Investigation

Warburg made a striking discovery in the 1920s that, even in the presence of ample oxygen, cancer cells prefer to metabolize glucose through non-oxidative pathways (aerobic glycolysis) – Warburg effect



This insight has yielded seminal practical applications such as FDG PET for tumor imaging



However, for many years, Warburg effect largely viewed as a reflection of a function of the hypoxic tumor environment

Research continued but was eventually eclipsed by a captivating finding from a parallel track of cancer investigation .....

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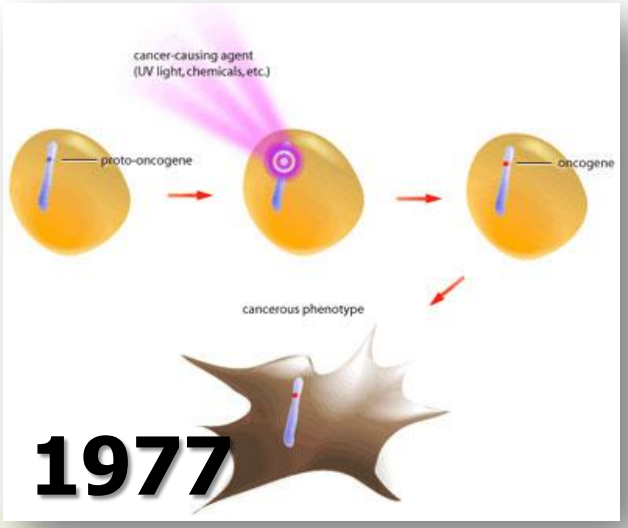
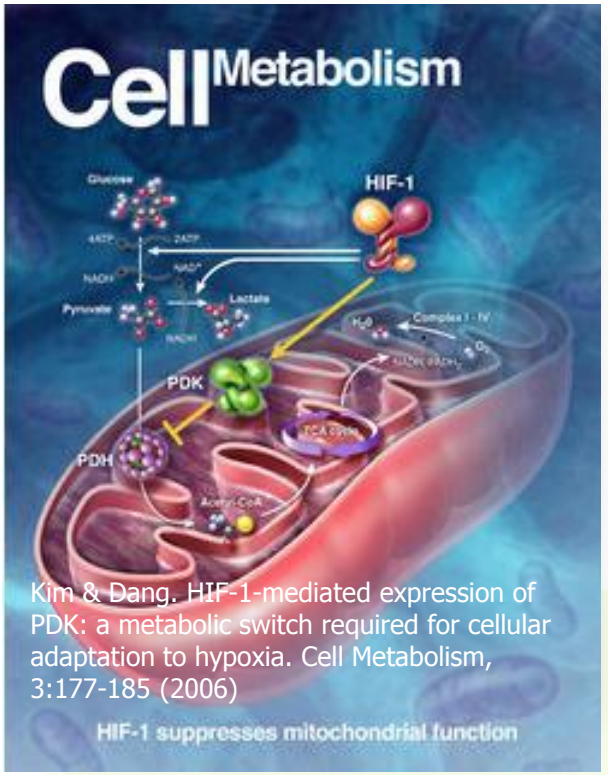
Molecular Biology Explosion Eclipses Metabolic Inquiry

Peyton Rous isolated the first oncovirus (avian sarcoma virus)



Bishop & Varmus discovered that the these oncoviral genes were actually mutated host genes – "Oncogenes"



Kim & Dang. HIF-1-mediated expression of PDK: a metabolic switch required for cellular adaptation to hypoxia. Cell Metabolism, 3:177-185 (2006)

- Upon the discovery of oncogenes, the molecular biology explosion surpassed Warburg's line of inquiry for all but a small group of investigators
- Eventually, a realization that Warburg's findings and cancer activating mutations were intimately connected

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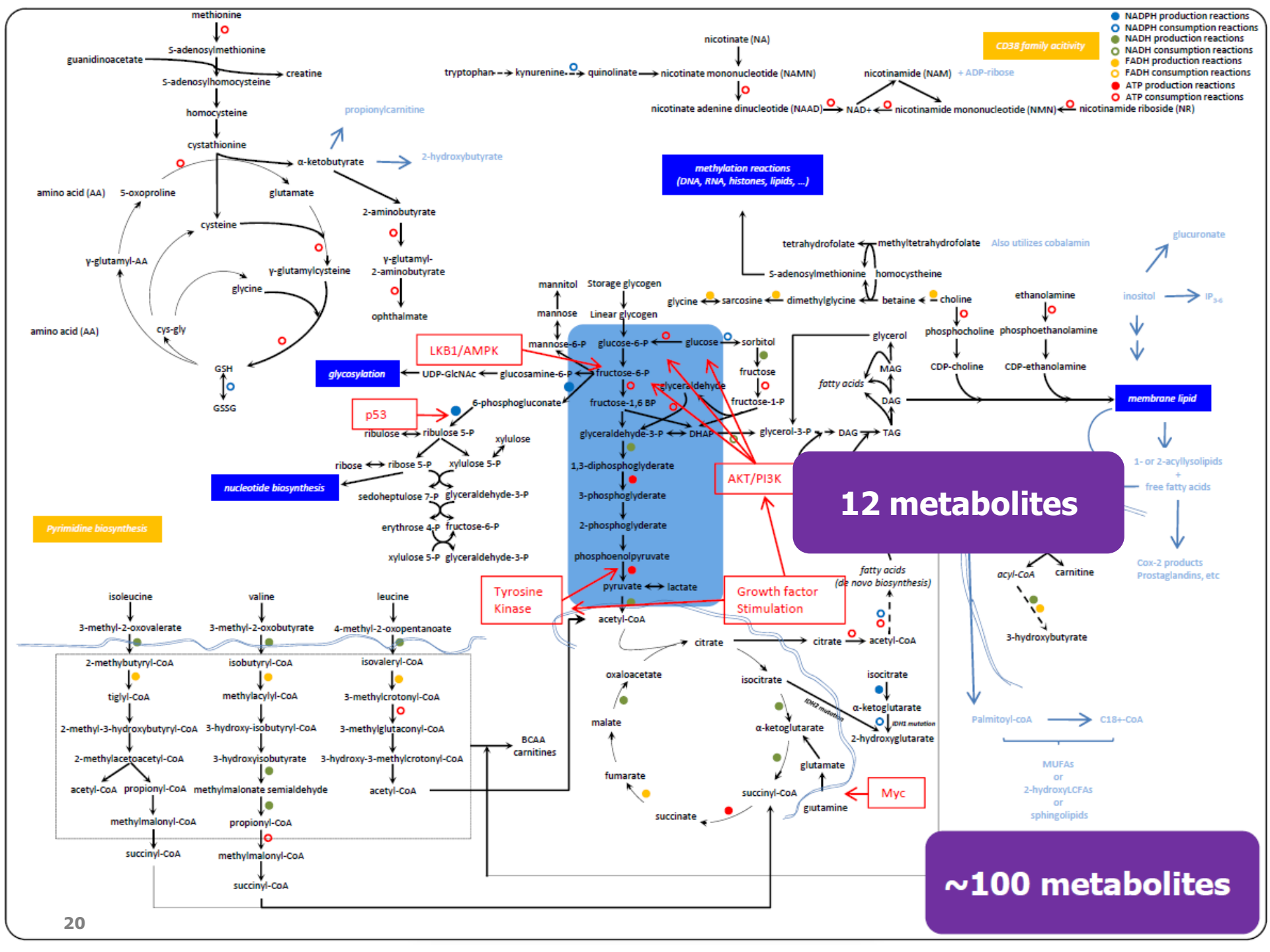
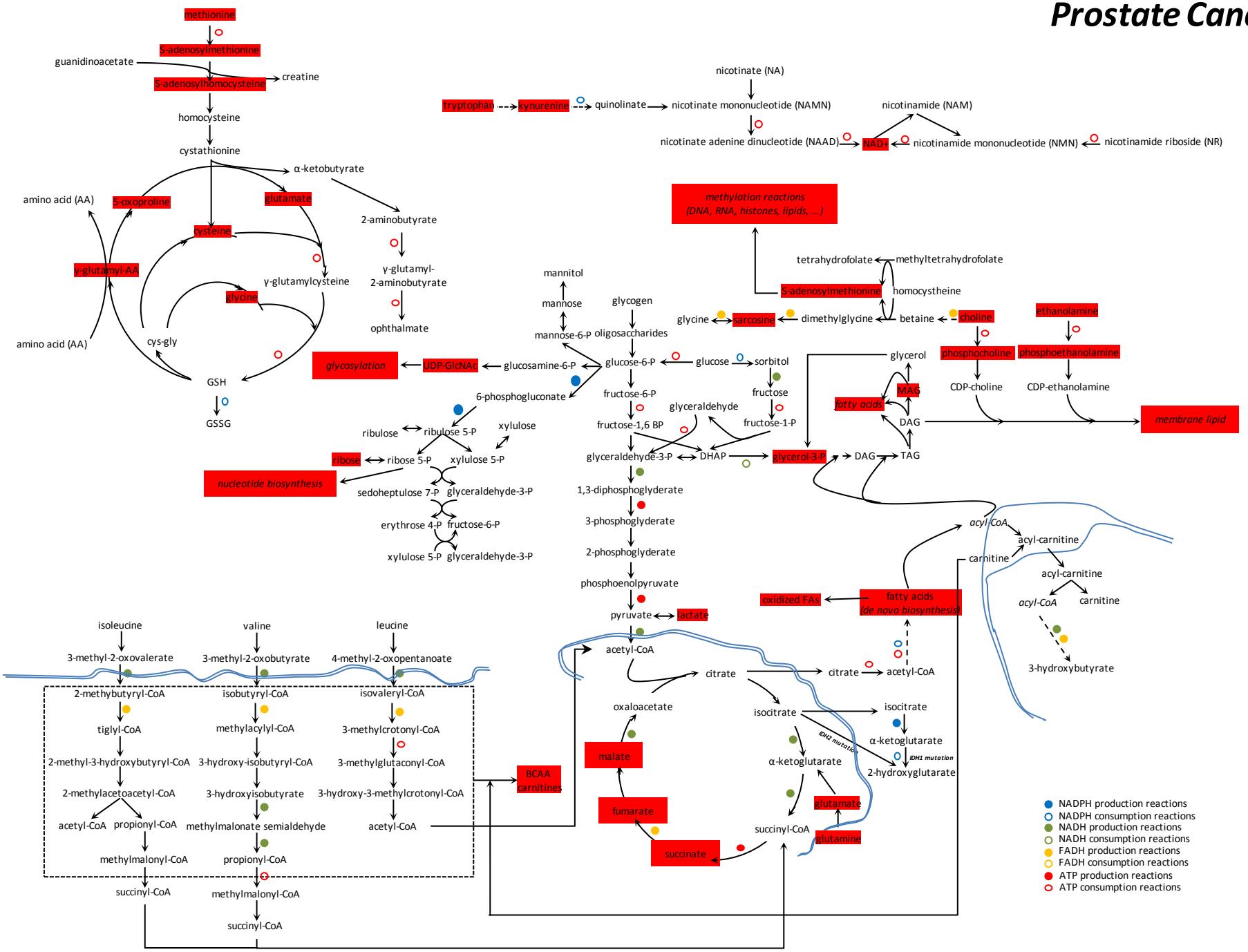

NADPH production reactions
NADPH consumption reactions
NADH production reactions
NADH consumption reactions
FADH production reactions
FADH consumption reactions
ATP production reactions
ATP consumption reactions
CD38 family acitivity
methionine
S-adenosylmethionine
guanidinoacetate
creatine
S-adenosylhomocysteine
homocysteine
cystathionine
propionylcarnitine
α-ketobutyrate
2-hydroxybutyrate
amino acid (AA)
5-oxoproline
glutamate
2-aminobutyrate
cysteine
γ-glutamyl-AA
γ-glutamylcysteine
γ-glutamyl-2-aminobutyrate
glycine
ophthalmate
amino acid (AA)
cys-gly
GSH
GSSG
nicotinate (NA)
tryptophan
kynurenine
quinolinate
nicotinate mononucleotide (NAMN)
nicotinamide (NAM)
+ ADP-ribose
nicotinate adenine dinucleotide (NAAD)
NAD+
nicotinamide mononucleotide (NMN)
nicotinamide riboside (NR)
methylation reactions
(DNA, RNA, histones, lipids, ...)
tetrahydrofolate
methyltetrahydrofolate
Also utilizes cobalamin
S-adenosylmethionine
homocystheine
glycine
sarcosine
dimethylglycine
betaine
choline
glucuronate
inositol
IP3-6
ethanolamine
phosphocholine
phosphoethanolamine
CDP-choline
CDP-ethanolamine
mannitol
Storage glycogen
mannose
Linear glycogen
LKB1/AMPK
glycosylation
UDP-GlcNAc
glucosamine-6-P
mannose-6-P
glucose-6-P
glucose
sorbitol
fructose
fructose-6-P
fructose-1-P
glyceraldehyde
6-phosphogluconate
fructose-1,6 BP
p53
glycerol
MAG
fatty acids
DAG
TAG
membrane lipid
ribulose
ribulose 5-P
xylulose
ribose
ribose 5-P
xylulose 5-P
nucleotide biosynthesis
sedoheptulose 7-P
glyceraldehyde-3-P
glyceraldehyde-3-P
DHAP
glycerol-3-P
1,3-diphosphoglyderate
AKT/PI3K
3-phosphoglyderate
2-phosphoglyderate
1- or 2-acyllysolipids
+
free fatty acids
Pyrimidine biosynthesis
erythrose 4-P
fructose-6-P
xylulose 5-P
glyceraldehyde-3-P
phosphoenolpyruvate
pyruvate
lactate
fatty acids
(de novo biosynthesis)
acyl-CoA
carnitine
Cox-2 products
Prostaglandins, etc
Tyrosine Kinase
Growth factor Stimulation
acetyl-CoA
citrate
acetyl-CoA
3-hydroxybutyrate
isoleucine
valine
leucine
3-methyl-2-oxovalerate
3-methyl-2-oxobutyrate
4-methyl-2-oxopentanoate
oxaloacetate
isocitrate
isocitrate
2-methylbutyryl-CoA
isobutyryl-CoA
isovaleryl-CoA
malate
α-ketoglutarate
α-ketoglutarate
IDH2 mutation
IDH1 mutation
2-hydroxyglutarate
tiglyl-CoA
methylacrylyl-CoA
3-methylcrotonyl-CoA
Palmitoyl-CoA
C18+-CoA
2-methyl-3-hydroxybutyryl-CoA
3-hydroxy-isobutyryl-CoA
3-methylglutaconyl-CoA
BCAA
carnitines
2-methylacetoacetyl-CoA
3-hydroxyisobutyrate
3-hydroxy-3-methylcrotonyl-CoA
fumarate
glutamate
acetyl-CoA
propionyl-CoA
methylmalonate semialdehyde
acetyl-CoA
succinyl-CoA
Myc
MUFAs
or
2-hydroxyLCFAs
or
sphingolipids
methylmalonyl-CoA
propionyl-CoA
succinate
glutamine
succinyl-CoA
methylmalonyl-CoA
succinyl-CoA
12 metabolites
~100 metabolites

Prostate Cancer



Diagnostics Product Pipeline

Diagnostic Product	Indication / Estimated Annual Market Size	Business Case	Feasibility	Validation	CLIA Ready	Market Ready*
Prostarix™DRE	Guide prostate biopsy decision / $600 mil.					2012
Prostarix	Prostate cancer aggression / $619 mil.					2012
Vasicar™	Bladder cancer aggression / $168 mil.					2013
Cisplatin toxicity	Cisplatin treatment tolerance / $200 mil.					2013
Renal Cell Carcinoma aggressiveness	Kidney cancer aggression/ $70 mil.					2013

* Commercial launch is pending financing

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Company Summary

- Validated, pioneering, patented technology poised to transform disease treatment and diagnosis
- Over the past 5 years, rapidly growing metabolytics business. 320 studies completed in 2010 processing over 33,000 samples. +60m in bookings since inception.
- Technology and know-how applied to develop a robust diagnostics pipeline targeting the largest healthcare disease categories.
- Large scale biology studies (clinical, GWAS) started in 2009.

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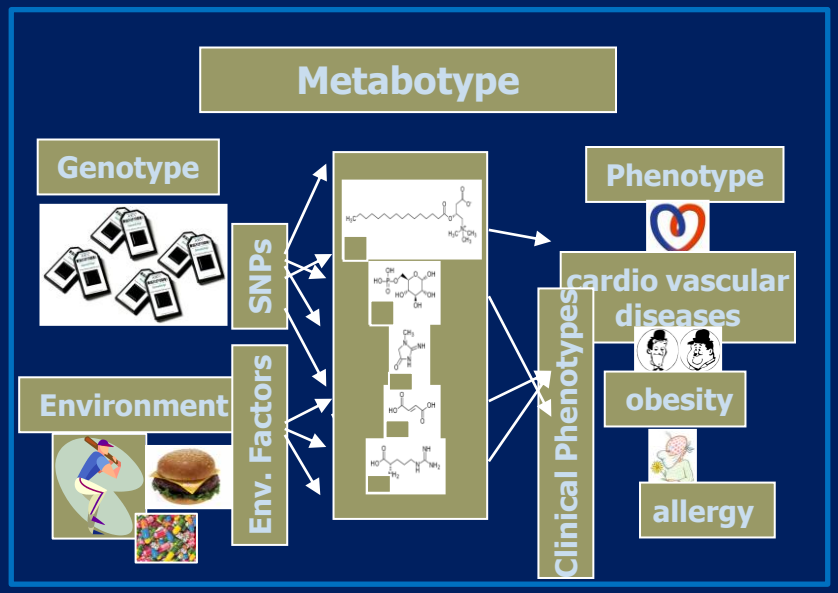
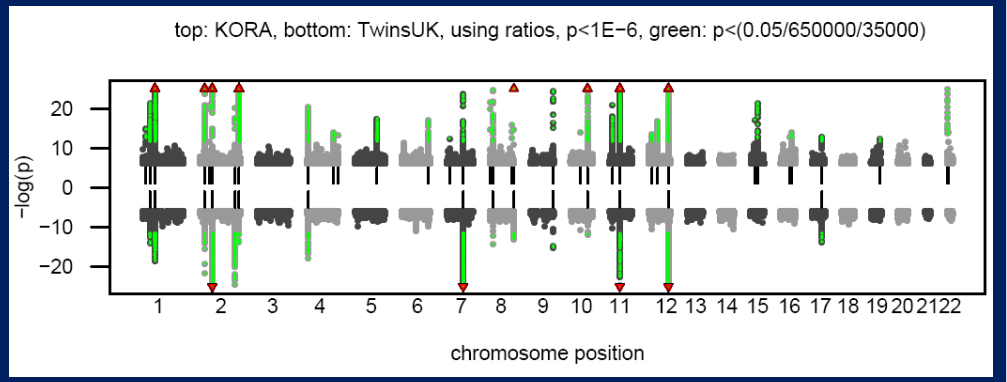
Metabolon GWAS Study

Nature 477, Pages: 54–60 Sep 1st, 2011

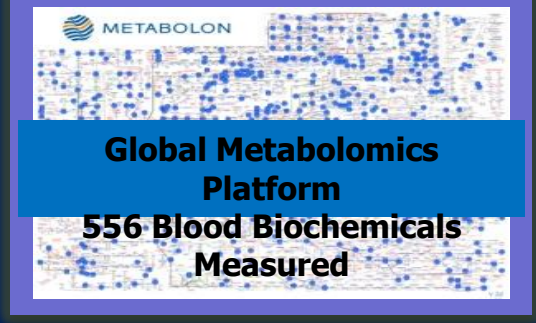
Study Rationale:
Using Metabolon's Global Metabolomics to Phenotype Two Large Genomic Studies

28 genomewide significant associations to biochemicals ($p<2x10^{-12}$) in the discovery study
-> 27 fully replicated in second study ($p<2x10^{-5}$)





- **KORA Genomic Study**
- 1,768 individuals
- 655,658 autosomal SNPs
- **TwinsUK:** (Merlin) Genomic Study
- 1056 individuals
- 534,665 autosomal SNPs



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